Antipsychotic augmentation of serotonergic antidepressants in treatment-resistant obsessive-compulsive disorder: a meta-analysis of the randomized controlled trials

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CRD summary
This review found that antipsychotic drugs added to antidepressants are more effective than antidepressants plus placebo for reducing symptoms in patients with treatment-resistant obsessive compulsive disorder. The conclusion reflects the evidence presented but is limited by the small number and size of the available trials. The authors' recommendation for further trials with more participants and using standard drug doses appears appropriate.

Authors' objectives
To determine the effectiveness of antipsychotic augmentation of serotonergic antidepressant therapy in patients with treatment-resistant obsessive compulsive disorder (OCD).

Searching
PubMed (1966 to January 2006), EMBASE (1980 to 2005), the Cochrane Controlled Trials Register (Issue 1, 2006) and PsiTri were searched; the search terms were reported. The reference lists of previous reviews and trial reports were also checked. No language restrictions were imposed.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Crossover studies were excluded.

Specific interventions included in the review
Studies of antipsychotic drugs used in combination with antidepressants were eligible for the review. The antipsychotics used in the included studies were haloperidol, risperidone, olanzapine and quetiapine. Patients in most studies received antidepressants (details reported) for 8 or 12 weeks before randomisation to antipsychotic or placebo. Studies of less than 4 weeks' duration were excluded; the duration of the included studies ranged from 4 to 16 weeks.

Participants included in the review
Participants were patients with OCD non-responsive (normally defined as a <35% or <25% improvement on the Yale-Brown Obsessive Compulsive Scale, Y-BOCS) to previous antidepressant treatment. Studies of patients with co-morbid schizophrenia or other psychotic disorders were excluded. In the included studies, the mean age of the patients ranged from 28 to 44 years and the proportion of men ranged from 25 to 76%.

Outcomes assessed in the review
Studies were required to report on symptoms assessed with the Y-BOCS or clinical response assessed with the Clinical Global Impressions-Improvement Scale (CGI-I).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed using a modified version of the Jadad scale; one point was deducted from the score if losses to follow-up exceeded 20%. Studies scoring 2 or less out of 5 were considered low quality, while those scoring 3 or more were considered acceptable. Two reviewers assessed validity.

Data extraction
One reviewer extracted the data and another reviewer checked the extraction. Data on numbers of patients responding to treatment in each group were used to calculate rate ratios (RRs) and 95%
confidence intervals (CIs) for each study.

**Methods of synthesis**

**How were the studies combined?**
The studies were combined by meta-analysis using fixed-effect or random-effects models; a random-effects model was used if significant heterogeneity was present.

**How were differences between studies investigated?**
Statistical heterogeneity was assessed using the chi-squared and I-squared statistics. Subgroup analyses were performed to assess the effect of type of antipsychotic drug used, definition of non-response to treatment, inclusion or exclusion of patients with co-morbid tic disorders, dose of antipsychotic medication used and trial duration. A sensitivity analysis was performed to investigate the effect of study quality.

**Results of the review**
Ten studies with 305 participants were included.

Across all 10 RCTs, treatment response was significantly more likely in patients receiving antipsychotic drugs than in those receiving placebo (RR 3.31, 95% CI: 1.40, 7.84), but statistical heterogeneity was significant. Studies with risperidone showed a significant positive effect (3 studies, pooled RR 3.89, 95% CI: 1.25, 12.05; heterogeneity was not significant), while those with olanzapine and quetiapine did not. Haloperidol showed a significant positive effect in one study (n=34). Studies that defined non-response as a 25% improvement or less on the Y-BOCS did not show a significant effect of antipsychotic augmentation, while those that used the 35% criterion did show a significant effect. Significant effects were seen with high but not low doses of antipsychotic drugs, in studies that excluded patients with tic disorders but not in those that included them, and in studies of 8 weeks or more but not in shorter studies. Only one study scored 2 or less on the modified Jadad scale; omitting this study gave a reduced but still statistically significant pooled RR of 2.78 (95% CI: 1.21, 6.37).

**Authors' conclusions**
The review supports the use of antipsychotic drugs as an augmentation strategy, but more and larger trials are needed.

**CRD commentary**
This review addressed a clear question and the inclusion and exclusion criteria were clear. The authors searched a reasonable range of sources without language restrictions. There was no systematic search for unpublished studies and the risk of publication bias was not assessed. Validity was assessed using a standard method and the results were used in a sensitivity analysis. Measures were taken to minimise reviewer errors and bias in the validity assessment and data extraction, although it is unclear whether similar methods were used at the study selection stage.

Adequate details of the included studies were presented in the text and tables. The studies were combined by meta-analysis. Statistical heterogeneity was assessed and appropriate subgroup analyses were performed. The authors' conclusions and recommendations for practice are in line with the evidence presented, but should be treated with caution because of the small numbers of studies and patients involved. The authors' recommendations for further research appear appropriate.

**Implications of the review for practice and research**
Practice: The authors stated that the results of the review support the use of risperidone as a first-choice and haloperidol as a second-choice antipsychotic drug in the short-term management of patients with treatment-resistant OCD.

Research: The authors stated the need for larger and longer term trials of antipsychotic drugs in patients with treatment-resistant OCD. Trials should avoid using low drug doses and should evaluate participants for the presence of co-morbid tic disorders.
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